

Human Infections Associated with *Bordetella bronchiseptica*

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INTRODUCTION

Although *Bordetella bronchiseptica* is said to be commonly encountered as both a commensal and a cause of respiratory tract disease in many wild and domestic animals, it has rarely been implicated as a cause of infection in humans. The purpose of this paper is to present a critical review of the literature in which human infections with *B. bronchiseptica* have been reported. First, the bacteriologic and pathologic characteristics of the microorganism are described. Second, its role as a commensal and as a human pathogen is examined. Data from two patients from whom we isolated *B. bronchiseptica* are included in the review.

BACTERIOLOGY OF *B. BRONCHISEPTICA*

Bacteriological Characteristics of *Bordetellae*

The genus *Bordetella* comprises three species, *B. pertussis*, *B. parapertussis*, and *B. bronchiseptica*. The microbiological characteristics that distinguish the three species are summarized in Table 1. A fourth species, *Bordetella avium*, has been proposed by Kersters et al. (93). This putative species, a cause of turkey coryza, closely resembles *Alcaligenes faecalis* and is not yet distinctly differentiated from it (113).

Bordetella pertussis, the major cause of whooping cough, was characterized by Bordet and Gengou (18) in 1906. Bradford and Slavin (19) in 1937 and Eldering and Kendrick (52) in 1938 distinguished *B. parapertussis* from *B. pertussis* because the former grew more rapidly on primary isolation, was oxidase negative, and produced pigment on tyrosine agar. They incriminated *B. parapertussis* as a minor cause of whooping cough, particularly a milder form than that caused by *B. pertussis*. Both species are extremely fastidious, requiring direct inoculation of nasopharyngeal swab material onto special media such as Bordet-Gengou (18) or Regan-Lowe (137) for primary isolation. Recent evidence such as the dual isolation of *B. pertussis* and *B. parapertussis* from

whooping cough patients (102) and the apparent conversion of *B. pertussis* to *B. parapertussis* by loss of a lysogenic bacteriophage (77) casts doubt on the validity of designating *B. parapertussis* as a separate species.

Ferry (61-63), using the name *Bacillus bronchisepticus*; McGowan (111), using the term *Bacillus bronchicanis*; and Torrey and Rahe (161), using Ferry's epithet, independently observed the association of a small gram-negative coccobacillus with outbreaks of "canine distemper" and respiratory tract illness in laboratory animals such as the cat, rabbit, and guinea pig. Because it was known later by a variety of names such as *Haemophilus bronchiseptica* (134), *Brucella bronchiseptica* (134), *Bacillus suisepicus* (44), *Alcaligenes bronchicanis* (134), and *Alcaligenes bronchisepticus* (134), the microorganism's taxonomic status and etiologic role in disease were hampered by both the state of the evolving microbiology and its commensal or opportunistic field of involvement in then poorly understood viral infections such as distemper (2, 48, 99, 159, 169). In 1952, Lopez (104) proposed that the bacterium be placed in the genus *Bordetella*, and thus it was assigned as *B. bronchiseptica* in the seventh edition of *Bergey's Manual of Systematic Bacteriology* (20). However, until the studies of Johnson and Sneath in 1973 (89) and Bemis et al. (11) in 1977, the microorganism was not well distinguished from certain phenotypically similar isolates, particularly some members of the genera *Acinetobacter*, *Achromobacter*, *Alcaligenes*, *Pseudomonas*, and *Brucella*. The morphological and biochemical characteristics of *B. bronchiseptica* are now considered to be as follows. It is an obligate aerobe, grows readily on simple nutritive media as small circular glistening or rough colonies 0.5 to 1.0 mm in diameter after 48 h of incubation in air at 35°C, is gram negative, and exhibits small bacillary morphology with peritrichous flagella. It is positive in tests for catalase, oxidase, citrate utilization, motility, urease, nitrate reduction, tetrazolium reduction, and growth on salmonella-shigella agar, and it is negative in tests for indole, acid production in oxidation-fermentation glucose and maltose media, tyrosine hydrolysis, and growth on tellurite agar. Although most isolates reduce nitrate and are motile, exceptions occur (11, 133, 166). Motility is best demonstrated in semisolid agar at 30°C. *B. bronchiseptica* can be conve-

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TABLE 1. Microbiological characteristics of *Bordetella* species

Characteristic	<i>B. bronchiseptica</i>	<i>B. pertussis</i>	<i>B. parapertussis</i>
Motility	+	—	—
Nitrate reduction	+	—	—
Rapid urease production	+	—	—
Oxidase	+	+	—
Growth on Bordet-Gengou agar (days)	1–1.5	3–4	1–2
Growth on heart infusion agar	+	—	+
Primary growth on blood agar	+	—	+

niently distinguished from phenotypically similar microorganisms by using the criteria of oxidase activity, urea hydrolysis, citrate utilization, tetrazolium reduction, growth on salmonella-shigella agar, and failure to grow on potassium tellurite medium. Commercially available identification systems such as the Rapid NFT (API System SA, Montalieu-Vercieu, France) (3), the API-ZYM (Analytab Products, Plainview, N.Y.) (79), and the Corning N/F system (Corning Medical Products, Roslyn, N.Y.) (7) have also been described as providing reliable identification.

Antimicrobial Susceptibility of *B. bronchiseptica*

A summary of several recent studies (4, 11, 60, 98, 115, 135, 155, 170) on the in vitro susceptibility of *B. bronchiseptica* to a number of antimicrobial agents is presented in Table 2. Although some discrepancies exist among the studies, probably as the result of methodologic differences, the response to a number of agents appears to be predictable and similar to that expected for nonfermentative gram-negative bacilli, particularly *Pseudomonas aeruginosa*. The aminoglycosides (amikacin, gentamicin, and tobramycin) appear to be highly effective in vitro against *B. bronchiseptica*, whereas streptomycin (11, 60) appears to be generally ineffective. The antipseudomonal penicillins azlocillin, mezlocillin, piperacillin, and ticarcillin also show a near 100% effectiveness in vitro, whereas the primary penicillins, ampicillin and penicillin G, appear to be considerably less effective although MICs, especially of ampicillin, could be considered as representing low-level resistance. Near 100% effectiveness is also exhibited in vitro for the antipseudomonal broad-spectrum cephalosporins, cefoperazone and ceftazidime, whereas other broad-spectrum cephalosporins show a broad variability of effectiveness. Expanded- and narrow-spectrum cephalosporins are largely ineffective in vitro. The tetracyclines each appear to be completely effective, with minocycline showing the lowest MICs of those agents tested. The MICs of the quinolones ciprofloxacin and ofloxacin appear near the susceptibility breakpoints, indicating that effective serum concentrations should be achieved by administering the drug intravenously or in higher dosages. Both chloramphenicol and imipenem appear to be effective. Trimethoprim-sulfamethoxazole and rifampin show variable effectiveness. As expected for other gram-negative microorganisms, the macrolides clindamycin and erythromycin appear totally ineffective.

After isolation, *B. bronchiseptica* grows readily on Mueller-Hinton agar and in Mueller-Hinton broth, thus making it likely that disk agar diffusion, agar dilution, and broth dilution susceptibility test methods should produce acceptable results, using the recommendations of the National

Committee for Clinical Laboratory Standards for gram-negative aerobic bacilli (122, 123). Discrepancies in susceptibility test results for the studies summarized in Table 2 are not readily explainable but may represent differences in the populations of strains tested, methodological variations, or both. In our assays, a significant difference in susceptibility test results for several antimicrobial agents (ampicillin, carbenicillin, ticarcillin, cephalosporins, and trimethoprim-sulfamethoxazole) was found for the Vitek AMS System (Vitek Systems, Hazelwood, Mo.) compared with the standard microbroth dilution method. These results support the Vitek AMS recommendation for confirming susceptibility of *B. bronchiseptica* by another method.

PATHOLOGY OF *B. BRONCHISEPTICA* INFECTIONS

Information on the pathological changes associated with *B. bronchiseptica* infection is essentially limited to the inferences that may be gained from animal studies and from autopsy studies on humans who died from complications of *B. pertussis* infections. There is a paucity of information on specific pathological findings in humans infected with *B. bronchiseptica*. Although *B. bronchiseptica* is thought to cause disease in a wide variety of domestic and wild animals, field and experimental observations have involved primarily dogs, swine, and rabbits. A brief summary of the pathology and pathogenesis of human and animal bordetellosis follows.

The role of *B. bronchiseptica* as a cause of respiratory tract infections in dogs was not convincingly established until the reports of Wright and colleagues (171) and others (8–10, 12, 73, 158, 160) some five decades after the initial independent observations of Ferry (61–65), McGowan (111), and Torrey and Rahe (161). On the basis of recent studies using the most stringent conditions (11, 89) for *B. bronchiseptica* identification, it is now fully established that *B. bronchiseptica* is the cause of an infectious tracheobronchitis in dogs known as “kennel cough.” In dogs, the infectious process is largely limited to the tracheobronchial tree and is characterized by adherence and localization of the bacteria to the cilia and surface structures of respiratory epithelial cells. The microorganisms adhering to the surface of cilia are best demonstrated by thin tissue sections stained with toluidine blue (12). The infection is accompanied by mild infiltration of neutrophils and lymphocytes in the submucosa and by moderate hyperplasia of adjacent lymphoid tissues (12, 159). These findings are similar to those described in early studies comparing the pathological changes in canine bordetellosis with those observed in autopsy studies of patients who died with complications of whooping cough (107–109, 138). Mallory et al. (107–109) proposed that the bacteria cause mechanical blocking of the respiratory cilia, resulting in failure of the respiratory tract to clear mucus secretions. Bacterial adherence and ciliostasis has since been demonstrated by others as well (14, 36, 45–47, 110, 162, 165). Corroborating evidence for the differential tropism and adherence of *Bordetella* species to respiratory epithelial cells has also come from in vitro studies (88, 97, 119, 162). Tuomanen and associates (162) showed that *B. pertussis* adheres preferentially to human ciliated respiratory tract cells, whereas *B. bronchiseptica* adheres preferentially to those of rabbits, mice, and hamsters. This differential tropism and adherence are thought to be related to those properties of the *Bordetella* species that cause agglutination of erythrocytes from a variety of mammals and fowls (11, 13, 71, 88, 92).

The mechanisms responsible for damage to cilia, epithe-

TABLE 2. Antimicrobial susceptibility patterns of *B. bronchiseptica*

Antimicrobial agent (susceptibility break- point, µg/ml) ^a	% Susceptible or MIC ₉₀ ^b (µg/ml) [range] for designated investigators							Woolfrey and Moody (present study), n = 12 ^h	
	Bemis et al. (11), n = 50 ^{c,d}	Fass and Bar- nishan (60), n = 10 ^{e,f}	Appelbaum et al. (4), n = 13 ^g	Strandberg et al. (155), n = 5 ^g	Kurzynski et al. (98), n = 11 ^g	Pijpers et al. (135), n = 20 ^g	Mortensen et al. (115), n = 48 ^e	MBD ^e	Vitek ⁱ
Aminoglycosides									
Amikacin (≤32)		100%		100%			100%	100%	100%
Gentamicin (≤8)	98%	100%		100%			>8 [1->8]	100%	100%
Tobramycin (≤8)		100%					100%	100%	100%
Penicillins									
Penicillin (≤2)	0%	0%					0%		
Ampicillin (≤16)	76%	16 [16-64]				90%	>16 [4->16]		
Ticarcillin (≤64)		100%					64 [≤4->64]	92%	83%
Mezlocillin (≤64)		100%					16 [≤4->64]	100%	
Piperacillin (≤64)		100%					100%	100%	
Azlocillin (≤64)							100%	100%	
Cephalosporins									
Cephalothin (≤16)	60%	100%	16 [1-32]					100%	17%
Cefazolin (≤16)		64 [16-128]						0%	0%
Cefamandole (≤16)		16 [16-32]							
Cefuroxime (≤16)		0%					0%	0%	
Cefoperazone (≤32)				100%			100%	100%	
Cefotaxime (≤32)		0%					>32 [≤2->32]	0%	
Ceftazidime (≤16)			100%	≥128 [4->128]			16 [2->32]	67%	
Ceftizoxime (≤32)								0%	
Ceftriaxone (≤32)			64 [0.5-64]	>32 [8->32]			>32 [≤0.5->32]	17%	50%
Tetracyclines									
Tetracycline (≤8)	100%	100%			0%	90%	100%	100%	100%
Doxycycline (≤8)		100%				95%			
Minocycline (≤8)		100%				100%			
Quinolones									
Ciprofloxacin (≤2)					4 [1-4]	100%		100%	100%
Ofloxacin (≤2)					0%	100%			
Miscellaneous									
Aztreonam (≤16)			>64 [4->64]	0%					
Chloramphenicol (≤16)	100%	100%				90%		100%	100%
Clindamycin (≤32)		0%							
Erythromycin (≤4)		8 [4-16]					>8 [1->8]		
Imipenem (≤8)				100%					
Rifampin (≤2)					0%		100%	83%	67%
Trimethoprim-sulfa- methoxazole (≤2/38)	66%	0.5/95 [0.5/ 9.5-128/ 2,432]			82%		4/76 [≤0.5/ 9.5->32/ 608]		

^a Susceptibility breakpoints represent those currently recommended by the National Committee for Clinical Laboratory Standards (122) for gram-negative bacilli.

^b MICs at which 90% of strains are susceptible.

^c Number of strains tested.

^d Disk agar diffusion method.

^e Microbroth dilution method.

^f Data represent either percent susceptible or median MIC.

^g Agar dilution method.

^h The 12 strains in the present study comprised two from our own cases (cases 1 and 2); one obtained through the courtesy of J. Snell, Central Public Health Laboratory, London, England, representing case 10; three kindly supplied by W. Fredericksen, Statens Seruminstitut, Copenhagen, Denmark, representing cases 14 to 16; three obtained through the courtesy of Joel Mortensen, Philadelphia, Pa., representing strains that were thought not to be related to disease and were recovered as incidental isolates in respiratory tract specimens from children; and three referred through the courtesy of T. Kurzynski, Madison, Wis., representing incidental recoveries from human respiratory tract cultures for which clinical information was lacking.

ⁱ Vitek Automicrobic System.

lium, and deeper tissues are still poorly understood. The outer membrane of *Bordetella* species contains a lipopolysaccharide endotoxin that is similar in chemical composition and physiological effects to those of other gram-negative microorganisms (24, 50, 105). *Bordetella* species also pro-

duce potent heat-labile dermonecrotic toxins that cause skin necrosis when injected intradermally into rabbits (33, 37, 38, 56, 58, 80, 84, 85, 87, 116, 120, 126, 131, 164). The dermonecrotic toxin, a single-stranded protein molecule of molecular weight 145,000, possesses no agglutinating properties for

animal erythrocytes and is distinctly independent from lipopolysaccharide endotoxin (87). This toxin produces turbinate atrophy accompanied by bone loss and chronic inflammation when applied intranasally or injected parenterally into young swine. The *Bordetella* species are also known to secrete adenylate cyclase (31, 57, 86), a substance that interferes with bactericidal, secretory, and other physiological processes of epithelial cells. Unless complicated by superinfection or a secondary event such as laryngospasm, the pathological changes associated with human and canine bordetellosis appear to be self-limiting and completely resolve with time.

By the late 1960s, it seemed to be clearly established that *B. bronchiseptica* was the agent responsible for a syndrome in swine characterized by turbinate atrophy, snout deformity, pneumonia, and failure to thrive (5, 34, 44, 46, 49, 101, 141). Of special influence were the studies by Switzer and associates (47, 82, 141–143) in which the disease was produced by repeated inoculation of aerosolized cultures of *B. bronchiseptica* into the nares of young disease-free pigs. In both field and experimental studies, the pathological changes observed were those of a progressive atrophy of the turbinates with squamous and goblet cell metaplasia of the mucosa, a mild to moderate acute inflammatory reaction within the submucosa, and damage to the developing turbinate bones characterized by increased osteoclastic activity and fibrous metaplasia of osteoblasts. Damage to the turbinates was shown to be due to the action of a dermonecrotic toxin because turbinate atrophy was produced by either intranasal or parenteral injection of the toxin into young swine. The mechanism was thought to be related to disruption of the energy-coupled formation and deposition of calcium apatite in newly forming bone (24, 80, 82, 84, 85, 140). Observations against the acceptance of *B. bronchiseptica* as the cause of atrophic rhinitis were (i) the variable effectiveness of vaccine preparations (15, 16, 59, 70, 72, 74, 83, 129), (ii) the transient nature of the experimental disease unless maintained by repeated inoculation of the organism (1, 69, 103, 125, 130, 163), (iii) the ready isolation of the agent from healthy swine and as a common commensal or opportunist in animals with viral and other respiratory diseases (17, 69, 75, 76, 130, 143, 145, 147), and (iv) the detection of other potential pathogens such as *Pasteurella multocida* by more discriminative microbiological methods (69, 81, 125, 130, 149). With continued accumulation of new information during the past two decades, the blame for atrophic rhinitis has gradually shifted from *B. bronchiseptica* to *P. multocida* (6, 23, 29, 30, 33, 37, 41, 42, 54, 55, 66, 114, 118, 121, 127, 130, 135, 139, 144, 146, 148, 149, 156). Considerable evidence now indicates that *P. multocida* plays the major pathogenic role, with *B. bronchiseptica* possibly acting as a conditioning agent for induction of the disease process. Like *B. bronchiseptica*, *P. multocida* elaborates a dermonecrotic toxin that on repeated local application to swine turbinates or with parenteral administration causes progressive turbinate atrophy (30, 37, 42, 54, 55, 66, 121, 148, 150).

In a situation analogous to the developments in swine atrophic rhinitis, *B. bronchiseptica* was thought to be the probable cause of snuffles, otitis media, and tracheal bronchitis in rabbits and guinea pigs (64, 78, 106, 151, 152, 167, 168). Evidence now indicates that *P. multocida* is the major pathogen, with *B. bronchiseptica* possibly playing an inducing or opportunistic role (36, 39, 40, 117).

B. BRONCHISEPTICA AS A HUMAN COMMENSAL

In evaluating the reports of *B. bronchiseptica* recovered from humans, two problems must be considered. The first is that acceptable stringent standards for differentiating *B. bronchiseptica* from phenotypically similar microorganisms were not available until the studies of Johnson and Sneath (89) and Bemis and coworkers (11). Thus, it is difficult to be certain that microorganisms described in earlier reports were truly *B. bronchiseptica*. The second problem is determining whether the agent actually caused the disease process or whether it might have been recovered merely as a nonoffending colonizer or commensal. Direct information about the latter problem is not available from the literature since recovery of a microorganism from a healthy person seldom warrants a report. The following literature review provides some insight into the commensal role of *B. bronchiseptica* in humans.

McGowan (111) examined nasopharyngeal cultures of 13 animal caretakers and found *B. bronchiseptica* in only 1 (see case 25). Winsser (169) found that 1 animal caretaker was a chronic carrier (see case 18) and studied nasopharyngeal cultures from 23 other animal caretakers; none harbored *B. bronchiseptica*. Switzer and colleagues (157) examined nasopharyngeal cultures from 80 swine farmers and found no *B. bronchiseptica*. In a retrospective study of 565 gram-negative nonfermentative bacilli recovered from clinical specimens, Pedersen and colleagues (132) found 16 designated as *B. bronchiseptica*. Of these, 10 were isolated from sputum in small numbers; 1, from respiratory equipment; 1, from a lung biopsy; and 4, from undesignated sources. On review of clinical records, none were deemed to be of clinical significance. In a retrospective study of 336 gram-negative nonfermentative bacilli representing clinical isolates and submitted for susceptibility testing, Gardner and colleagues (67) found only 2 to have been identified as *B. bronchiseptica*. However, in a subsequent prospective study of 194 consecutive patients from whom gram-negative nonfermentative bacilli were isolated, *B. bronchiseptica* was found in 18. Of these 18 isolates, 16 were thought to represent nosocomial colonization (15 from sputum and 1 from urine), 1 was a nosocomially acquired septicemia (see case 11), and 1 was a nosocomially acquired tracheobronchitis (see case 12). In three studies of the in vitro antimicrobial susceptibility of nonfermentative gram-negative bacilli, 10 of 322 (60), 11 of 324 (4), and 5 of 159 (155) isolates are described as *B. bronchiseptica*, but no clinical information about the patient sources is provided. In our experience, before encountering the two isolates to be described later, of more than 3,000 nonfermentative gram-negative bacilli isolated in the St. Paul-Ramsey Medical Center Clinical Microbiology Laboratory, only 1 was designated as *B. bronchiseptica* (170). This microorganism was isolated in a culture of otherwise normal cerebrospinal fluid from a patient with a mild head injury who showed no signs of meningitis; the isolate was therefore considered to be a contaminant. In a recent study of the antimicrobial susceptibility patterns of 48 *B. bronchiseptica* strains, Mortensen and colleagues (115) mention three from human sources. Mortensen has indicated that the three strains were chance recoveries and not clinically important and that two additional strains have since been recovered from the respiratory tracts of children with cystic fibrosis (114a).

The rare recovery of *B. bronchiseptica* from humans is also supported by examining studies on the etiology of whooping cough (21, 32, 43, 53, 100, 102, 112, 124, 136) in

which optimal performance and close scrutiny of cultures would be expected. Of the collective thousands of cases, only one *B. bronchiseptica* isolate was reported to have been isolated, and the identity is of questionable validity, as discussed later (see case 13).

B. BRONCHISEPTICA ASSOCIATED WITH HUMAN INFECTIONS

A brief chronological summary of 25 human infections reported to be associated with *B. bronchiseptica* is presented in Table 3. Included are 2 of our cases and 23 obtained from a literature review. Of the 23 cases found in the literature, only four reports (see cases 4, 5, 7, and 8) presented sufficient microbiological data for reliable identification of the microorganism as *B. bronchiseptica*. However, for four of the cases (see cases 10 and 14 to 16) with insufficient microbiological data, we obtained subcultures of the stored microorganisms, each of which proved to be *B. bronchiseptica* on testing in our laboratory. A brief summary and analysis of each case follow.

Cases with Verified *B. bronchiseptica* Identification

As the result of a motorcycle accident, a 26-year-old male (case 1) suffered a C-4 vertebral fracture with trauma to the cervical spinal cord, producing an acute quadriplegia with some preservation of upper extremity motor function. On return to the surgical intensive care unit after an emergency decompression of the spinal cord, he was noted to be gagging and was thought to have aspirated gastric contents. Aspiration was confirmed by an emergency bronchoscopy, the tracheobronchial tree was cleared, and cultures of the material later grew a variety of both aerobic and anaerobic microorganisms. Following bronchoscopy the patient was intubated, placed on a respirator, and started on clindamycin and gentamicin therapy. On the following day a right lower lobe atelectasis and infiltrate were noted, temperature was elevated to 101 to 103°F (38.3 to 39.4°C) and a neutrophilic leukocytosis developed over the next few days, peaking at 21.4×10^3 leukocytes (WBC)/mm³ on the ninth postoperative day with a return to normal by day 16. Sputum specimens obtained by endotracheal aspirations on days 4 and 6 grew only oropharyngeal flora. An endotracheal sputum specimen obtained on day 9 grew >90% *B. bronchiseptica*. The microorganism was initially identified by the Vitek AMS and API 20E systems and was later confirmed by standard microbiological methods, using current stringent criteria (11, 89). Susceptibility testing by the Vitek AMS System showed the microorganism to be susceptible to amikacin, carbenicillin, ciprofloxacin, mezlocillin, piperacillin, and tobramycin and resistant to cefotaxime and ceftazidime. Because of persisting right lower lobe atelectasis and difficulty in clearing secretions, a therapeutic bronchoscopy was performed on day 10 from which cultures of bronchial washings grew >10⁵ CFU of *B. bronchiseptica* and 3×10^3 CFU of coagulase-negative staphylococci per ml. An endotracheal sputum specimen obtained on day 11 grew only oropharyngeal flora. Because of continuing problems with atelectasis and clearing of secretions, a tracheostomy was placed on day 12, and cultures of tracheobronchial secretions obtained during the procedure grew 100% *B. bronchiseptica*. On day 14, in response to the culture reports of *B. bronchiseptica*, antimicrobial therapy was changed to piperacillin, tobramycin, and vancomycin. In the week following placement of the tracheostomy and change of antimicrobial therapy, there

was an improvement in clinical status accompanied by a return of WBC and temperature to the normal range. However, a culture of endotracheal material obtained through the tracheostomy on day 20 grew >50% *B. bronchiseptica*. On day 25, after continuing improvement in clinical status, the patient was extubated and antimicrobial therapy was discontinued. During the next 2 weeks the patient's care was gradually transferred to the physical medicine and rehabilitation service without complications. Further respiratory tract cultures were not obtained. In this case the recovery of *B. bronchiseptica* from three respiratory tract specimens obtained during the height of clinical symptomatology and WBC elevation along with the improvement in clinical status following a change of antimicrobial therapy suggest a causal or at least a cocausal role for the agent. A history of contact with normal or sick animals was not elicited.

A 54-year-old male (case 2) presented to his local hospital emergency room suffering from a severe sore throat, cough, difficulty swallowing, and difficulty breathing. He was immediately treated with bronchodilators and the intravenous administration of corticosteroids and ampicillin. X-ray films of his neck showed signs of severe epiglottitis. Blood gas studies showed a significant hypoxia with a pO₂ of 52 mm Hg. The patient experienced a cardiorespiratory arrest. A normal sinus rhythm and spontaneous respiration resumed after CPR and placement of a tracheostomy tube. The patient was then transferred to St. Paul-Ramsey Medical Center for continued emergency care. On admission, the patient was neurologically unresponsive, showing generalized clonic/tonic movements. Except for a temperature of 103°F, vital signs were within normal limits. Indirect laryngoscopy revealed severe epiglottal and laryngeal edema. The patient failed to regain neurological function and remained on artificial ventilation throughout most of the subsequent hospital course. Admission laboratory studies were within normal limits except for WBC count of 30.2×10^3 /mm³ showing approximately 90% combined neutrophils and band forms. Blood gases and electrolytes were within normal limits except for a sodium of 134 meq/liter, potassium of 3.4 meq/liter, and glucose of 282 mg/dl. The patient was placed on intravenous cefotaxime and clindamycin, was given diltiazem and valproate, and, as a known diabetic, was maintained on NPH insulin. Four blood specimens drawn before the administration of antibiotics, and four subsequent blood specimens, were sterile. Urine specimens obtained on admission and 2 days later were sterile. Sputum cultures on admission and 2 days later showed a scanty growth of normal respiratory flora. On the fourth hospital day the patient was taken to the operating room for direct laryngoscopy. The tonsillar and peritonsillar areas were erythematous and swollen, and a defect in the lower pole of the left tonsil leading into the left lateral pharyngeal wall suggested the possibility of a previously expressed abscess. Pus was not obtainable by punctures of the hypopharyngeal area. The epiglottis was erythematous and swollen, with tissues at the base of the epiglottis and left false chord appearing necrotic and friable. A left tonsillectomy was performed and biopsies and cultures were taken from the base of the epiglottis, the lateral hypopharyngeal wall, and the tonsillar defect. Microscopic examination of the tonsil material showed partially ulcerated mucosa with acute and chronic inflammatory cells in the stroma. Sections of the other biopsies showed necrotic tissue with acute inflammation. Only one small portion of tissue showed respiratory tract epithelium, and bacteria associated with the ciliated epithelium were not demonstrated by careful search of Gram- and toluidine blue-stained

TABLE 3. Summary of reports mentioning *B. bronchiseptica* isolated from human infections

Case	Yr	Author(s) (reference)	Age (yr)	Sex	Infection	Compromised host	Animal contact	<i>B. bronchiseptica</i> confirmed
1	1990	Woolfrey and Moody	26	M	Nosocomial tracheo-bronchitis	Acute quadriplegia with aspiration	None	Yes (culture in authors' laboratory)
2	1988	Woolfrey and Moody	54	M	Acute maxillary sinusitis (possible acute epiglottitis)	Diabetic	None	Yes (culture in authors' laboratory and state health department)
3	1987	Buggy et al. (25)	55	M	Pneumonia	Leukemia	Swine	No (microbiological characteristics not described)
4	1987	Papasian et al. (128)	60	M	Pneumonia	Leukemia		Yes (acceptable microbiological characteristics described)
5	1984	Katzenstein et al. (91)	70	M	Septicemia	Alcoholic		Yes (acceptable microbiological characteristics described)
6	1981	Byrd et al. (26)	60	M	Peritonitis	Peritoneal dialysis	Pet dog	No (incomplete microbiological characteristics described)
7	1981	Stoll et al. (154)	26	F	Pneumonia	Hodgkins disease	Sick pet dog	Yes (acceptable microbiological characteristics described)
8	1979	Ghosh and Tranter (68)	70	M	Pneumonia	Alcoholic	None	Yes (acceptable microbiological characteristics described)
9	1975	Chang et al. (27)	9	M	Meningitis	Orbital fractures	Kicked by horse	No (microbiological characteristics not described)
10	1973	Snell (153)	Adult		Typhoid-like septicemia			Yes (referred lyophilized culture showed acceptable microbiological characteristics)
11	1970	Gardner et al. (67)	69	M	Pneumonia with septicemia	Post-op aortic valve replacement for endocarditis		No (incomplete microbiological characteristics described)
12	1970	Gardner et al. (67)	57	F	Nosocomial	Aortic valve replacement with post-op abdominal abscess		No (incomplete microbiological characteristics described)
13	1967	Brooksaler and Nelson (21)	12	M	Whooping cough	No	Sick pet rabbit	No (microbiological characteristics not described)
14	1962	Kristensen and Lautrop (96)	5	M	Whooping cough, 6 wk	No	Farm animals	Yes (referred lyophilized culture showed acceptable microbiological characteristics)
15	1962	Kristensen and Lautrop (96)	7	M	Whooping cough, 5 wk	No	Farm animals	Yes (referred lyophilized culture showed acceptable microbiological characteristics)
16	1962	Kristensen and Lautrop (96)	Child	M	Cough, 3 days	No	Farm animals	Yes (referred lyophilized culture showed acceptable microbiological characteristics)
17	1960	Dale and Geraci (35)	60	M	Bacteremia	Staphylococcal endocarditis		No (incomplete microbiological characteristics described)
18	1960	Winsser (169)	Adult	M	Paroxysmal cough	No	Animal caretaker	No (incomplete microbiological characteristics described)
19	1960	Winsser (169)	Not stated		Sinusitis			No (incomplete microbiological characteristics described)
20	1958	Krepler and Flamm (95)	14	M	Pneumonia	No		No (microbiological characteristics not described)
21	1950	Chang (28)	2	M	Whooping cough	No	No <i>B. bronchiseptica</i> isolated from pet dog	No (incomplete microbiological characteristics described)
22	1950	Jones (90)	Not stated		Endocarditis			No (microbiological characteristics not described)
23	1926	Brown (22)	5	F	Whooping cough	No	<i>B. bronchiseptica</i> isolated from pet rabbit	No (incomplete microbiological characteristics described)
24	1917	Ferry (65)	Adult	M	Details not stated	No	Laboratory guinea pigs	No (incomplete microbiological characteristics described)
25	1911	McGowan (111)	Adult	M	Catarrh	No	Animal caretaker	No (incomplete microbiological characteristics described)

thin tissue sections. Although the WBC and differential counts had returned to normal after the fourth hospital day, the patient's temperature remained elevated to 102°F (38.8°C). A CAT scan of the head showed bilateral opacification of the maxillary, sphenoid, and frontal sinuses with indications of air-fluid levels in the maxillary sinuses. On the 10th hospital day the maxillary sinuses were punctured and a small amount of inspissated material was aspirated from each for culture. Bilateral maxillary sinus windows were placed for drainage. Aerobic cultures of the left sinus material grew *Staphylococcus epidermidis* and *P. aeruginosa*. Aerobic cultures of the right maxillary sinus grew <10% *S. epidermidis* and >90% *B. bronchiseptica*. In our laboratory the isolate was identified as *B. bronchiseptica* with the API 20E (Analytab Products, Plainview, N.Y.), the Vitek Automatic System, and by standard microbiological tests (11, 89). The strain was also identified as *B. bronchiseptica* by the Minnesota State Department of Health Laboratories. Cultures of the sinus material for anaerobes, mycobacteria, and fungi were negative. By the Automatic System, the *B. bronchiseptica* isolate was susceptible to carbenicillin, gentamicin, tetracycline, tobramycin, and trimethoprim-sulfamethoxazole and was resistant to ampicillin, cefamandole, cefoxitin, cephalothin, and chloramphenicol. During the remainder of the hospitalization the patient continued to be febrile, and neurologic function was not restored. The patient died 4 weeks after admission and an autopsy was not performed. Aside from having a pet dog, there were no known animal contacts. In summary, although *B. bronchiseptica* appeared to play a pathogenic role in the acute maxillary sinusitis, its role in the acute laryngopharyngitis remains speculative. This case illustrates the difficulty in assigning pathogenic or commensal roles for *B. bronchiseptica* in the cases reviewed.

In the case described by Papasian and colleagues (128) the patient was a 60-year-old male (case 4) who presented with acute bronchitis and pneumonia. He was known to have had chronic lymphocytic leukemia for 6 years and was treated by splenectomy 3 years previously and recently by chemotherapy. Initial bilateral bronchial washings and catheter brush specimens, as well as sputum cultures obtained during a recrudescence 5 days later, grew large numbers of *B. bronchiseptica*, which was identified by API 20E and subsequently confirmed by the Missouri Department of Health. The initial episode of tracheobronchitis was apparently resolved by amikacin and cefazolin treatment; however, sputum cultures remained positive. The recrudescence was successfully treated with oral trimethoprim-sulfamethoxazole. The case appears to be that of a valid respiratory tract *B. bronchiseptica* infection in a compromised host.

Katzenstein and colleagues (91) described a 70-year-old male (case 5) with hepatic failure, gastrointestinal bleeding, and sickle cell traits, who developed septicemia on the 18th hospital day. *B. bronchiseptica* was recovered from multiple premortem blood cultures obtained on separate days and from postmortem liver and spleen cultures. The organism was identified by using the API 20E system and was confirmed by the Centers for Disease Control. At autopsy, except for the nonspecific signs of sepsis, an infectious focus was not found. The case appears to be that of a valid *B. bronchiseptica* sepsis in a compromised host.

Stoll and coworkers (154) described a 26-year-old female (case 7) with long-standing Hodgkins disease, who presented with pneumonia and pleural infection following chest tube placement for a developing pneumothorax. The patient's dog had died 5 days previously after developing rhinorrhea and a

cough. *Staphylococcus aureus* was isolated from one blood culture, and *S. aureus* and *B. bronchiseptica* were recovered from a sputum culture. The isolate was identified by using standard methods and appropriately stringent microbiological criteria (11, 89). Both the *S. aureus* and the *B. bronchiseptica* isolates were found to be susceptible to cefazolin. The recovery of *S. aureus* from both blood and sputum suggests that *S. aureus* was the major pathogen. The recovery of *B. bronchiseptica* from the sputum only suggests a superinfection or commensal role in a compromised host.

Ghosh and Tranter (68) described a 73-year-old male debilitated alcoholic (case 8) with bilateral pneumonia and right lung abscess from whom bronchoscopic and tracheal aspiration cultures grew mixed aerobic and anaerobic bacteria, including *B. bronchocanis*; the latter also was recovered from one blood culture. The isolate was identified by using standard methods and appropriately stringent microbiological criteria (11, 89). This case appears to be that of a valid *B. bronchiseptica* pneumonia and sepsis in a compromised host.

Snell (153) alluded to the use of a reference microorganism that he had identified as *B. bronchiseptica*. The microorganism was sent to him by Khaled (94), who had recovered it in a blood culture from a patient (case 10) with a typhoidlike syndrome. The microbiological characteristics and criteria for identification of the microorganism as *B. bronchiseptica* were not presented. Through the courtesy of J. J. S. Snell (Central Public Health Laboratory, London, England), we obtained a lyophilized sample of the original culture from the National Collection of Type Cultures. In our laboratory the isolate was identified as *B. bronchiseptica* by the API 20E and Vitek AMS systems and by standard microbiological methods (11, 89). The case appears to be that of a valid *B. bronchiseptica* septicemia in a host who was possibly compromised.

Kristensen and Lautrop (96) described a farm family in which the three younger children (cases 14 to 16) developed whooping cough symptoms shortly after the onset of a respiratory tract illness in some of their farm animals which resulted in the death of four of six rabbits and three of five cats. *B. bronchiseptica* was said to have been isolated from the nasopharyngeal secretions of a 5-year-old boy with whooping cough symptoms for 6 weeks, a 7-year-old boy with whooping cough symptoms for 5 weeks, an older boy with a cough for 3 days, three asymptomatic older siblings, and from two of the surviving cats. The microorganism was not recovered from the mother, father, or the three older siblings. *B. pertussis* and *B. parapertussis* were said to have been carefully looked for on Bordet-Gengou primary plates and were not found. Microbiological characteristics for identification included appropriate Gram stain and flagellar morphology; positive reactions for oxidase, motility, nitrate reduction, and urease; and no acid production from glucose. Lyophilized samples of the original cultures from four of the siblings were kindly supplied to us by Wilhelm Frederiksen, Statens Serum Institut, Copenhagen, Denmark; in our laboratory each was identified as *B. bronchiseptica* by the API 20E, API NFT, and Vitek AMS systems and by standard microbiological methods (11, 89). These cases appear to represent valid recoveries of *B. bronchiseptica* from humans; however, the causal role in disease is unclear. Although the syndrome resembled whooping cough, appropriate microbiological methods failed to detect *B. pertussis* and *B. parapertussis*. It is possible that the upper respiratory tract illnesses in the family were of viral etiology and that the recovery of *B. bronchiseptica* represented the incidental

detection of colonization in people closely exposed to sick farm animals.

Cases with Unverified *B. bronchiseptica* Identification

In the remaining 15 reports summarized below, the microbiological findings either were not presented or did not meet the currently accepted standards for *B. bronchiseptica* identification, the latter problem roughly paralleling the age of the report.

Buggy and colleagues (25) described a 55-year-old swine farmer (case 3) with chronic lymphocytic leukemia for 4 years who presented with an acute pneumonia responding to tetracycline. A relapse of the pneumonia 4 months later responded to erythromycin. *B. bronchiseptica* was isolated from two respiratory tract cultures during each episode. Unfortunately, no details were given as to the microbiological methods and criteria used for identification. Attempts by us to obtain subcultures of the original isolates from these cases were unsuccessful. The response of the second pneumonic episode to erythromycin weighs against *B. bronchiseptica* as a cause.

Byrd and coworkers (26) described a 60-year-old male dialysis patient (case 6) with signs of peritonitis, from whom a single peritoneal dialysis fluid culture yielded a gram-negative coccobacillus identified as *B. bronchiseptica* on the basis of positive catalase, oxidase, motility, nitrate reduction, and urease tests. The patient had had close contact with a pet dog during dialysis manipulations. Because of his failure to improve on intraperitoneal and intravenous gentamicin and cephalothin administered for 48 h, therapy was changed to intraperitoneal and intravenous chloramphenicol. Complete resolution of fever, abdominal pain, and turbidity of the dialysate resulted after 5 days. Susceptibility studies showed resistance to ampicillin, cephalothin, gentamicin, amikacin, and tobramycin and susceptibility to tetracycline, trimethoprim-sulfamethoxazole, and chloramphenicol. This uniform resistance to the aminoglycosides would be highly unusual for *B. bronchiseptica*.

Chang and colleagues (27) recovered *B. bronchiseptica* from two separate specimens of cerebrospinal fluid obtained from a 19-year-old boy (case 9) who developed signs and symptoms of meningitis following repair of an orbital fracture due to a horse kick. The patient completely recovered after treatment with chloramphenicol and methicillin administered intravenously for 9 days followed by intravenous ampicillin for 2 weeks. Cultures of the patient's cat, dog, and gerbils did not yield *B. bronchiseptica*. The microbiological methods and criteria for identification were not presented.

In a prospective study of 190 cases of whooping cough confirmed by either the fluorescent antibody test or culture, or both, Brooksaler and Nelson (21) found only one instance in which *B. bronchiseptica* was thought to have been isolated. This was an 8-year-old boy (case 13) who also had a sick rabbit. Characteristics for identification were not described, were not included in the cited references, and were not available on inquiry.

Dale and Geraci (35) briefly mentioned a 60-year-old male (case 17) with long-standing endocarditis from whom a CO₂-dependent *S. aureus* was recovered in 6 of 11 blood cultures; 3 of the positive cultures also grew a microorganism designated as *B. bronchiseptica*. Other than describing the microorganism as a small gram-negative motile bacillus requiring room temperature and increased CO₂ for isolation, other features were not described.

Winsser (169) briefly described the isolation of two *B.*

bronchiseptica strains from humans (cases 18 and 19). The first (strain VH) was repeatedly isolated from the throat of a young animal caretaker who, after a bout with pneumonia, had recurrent colds and a nonproductive cough resembling mild whooping cough paroxysms, especially before bedtime. *B. bronchiseptica* was not isolated from animals that he had worked with or from close family contacts. The second (strain CW) was said to have been isolated from a sinus of a symptomatic febrile human patient, but further details were not given. A reference animal strain (W.) to which strains VH and CW were compared was described as showing appropriate gram-negative and colonial morphology; positive reactions for oxidase, motility, citrate, and urease and negative reactions for indole and carbohydrate fermentation. The W. strain was said to produce disease on intranasal or intraperitoneal inoculation of mice and ferrets.

Krepler and Flamm (95) recovered *B. bronchiseptica* repeatedly from sputum cultures of a 14-year-old boy (case 20) with a pulmonary infiltrate and "subacute tuberculoid cavity" that responded well to tetracycline therapy. There was no known animal contact, and microbiological details were lacking.

Chang (28) described a 2-year-old boy (case 21) with whooping cough symptoms for 1 month from whom a microorganism, thought initially to be *B. pertussis*, was repeatedly isolated from nasopharyngeal cultures. The microorganism was not recovered from several nasal cultures of the patient's pet dog. The primary culture after 48 h on Bordet-Gengou medium showed numerous, pinhead-sized colonies that were smooth and glistening, with narrow zones of β -hemolysis, and were composed of gram-negative coccobacilli that were agglutinated with *B. pertussis* antiserum to a titer of 640. The microorganism was found to be positive for oxidase, motility, and nitrate reduction and negative for indole, gas and acid production from dextrose, lactose, maltose, and saccharose and was agglutinated by *B. bronchiseptica* antiserum to a titer of 10,000. Urease activity was not mentioned. Except for hemolysis, all findings were identical to those of a standard strain of *B. bronchiseptica* obtained from the American Type Culture Collection. The isolate was said to have been confirmed as *B. bronchiseptica* by Grace Eldering and is apparently the isolate mentioned by Eldering and colleagues (51) as the single *B. bronchiseptica* isolate in a large number of whooping cough cases observed over a 30-year period. Eldering's identification criteria were not described except that in serological studies the strain agglutinated weakly in *B. pertussis* and *B. parapertussis* antisera. During the illness the patient exhibited a marked lymphocytosis, a situation strongly suggesting that the whooping cough was actually caused by *B. pertussis* that was not detected in the primary cultures.

In a review of the literature of nonstreptococcal endocarditis, Jones (90) mentions finding a report (case 22) of *B. bronchiseptica* endocarditis but does not specifically cite the report. On review of the cited references, we were unable to confirm the existence of such a case.

Brown (22) described a 5-year-old girl (case 23) who was given a pet rabbit that developed snuffles and diarrhea. Twelve days after receiving the pet the child developed a night cough with paroxysms and a well-defined whoop gradually subsiding over a 1-month period. Chocolate agar cough plates obtained during paroxysms on two separate days showed 25 and 68%, respectively, colonies that were small, grey, semitransparent, and convex, showing gram-negative coccobacillary morphology. Premortem nares cultures and postmortem blood cultures of the rabbit were said

to grow pure cultures of the same microorganism. The isolates from the child and the rabbit were compared with a strain of *B. bronchiseptica* obtained from the stock collection of the Society of American Bacteriologists and were found to be alike in every respect. The isolates produced hemolysis on heavy inoculation, an ammoniacal odor, and an alkaline reaction in dextrose broth and were motile. Agglutination studies with sera of rabbits injected with isolates from the child, rabbit, and stock strain showed a common agglutination pattern for all strains and did not agglutinate a *B. pertussis* strain. In this case, the use of blood agar in the initial attempt at isolating a pathogen by cough plate inoculation probably accounts for the failure to recover either *B. pertussis* or *B. paraptussis*. In addition, at that time the latter organism was not recognized as a pathogen.

In an early report (65) and in a personal communication to Brown (22), Ferry described isolating *B. bronchiseptica* in pure culture from the sputum of a symptomatic adult male laboratory worker (case 24) who had been exposed to guinea pigs with *B. bronchiseptica* infection. The microbiological characteristics of the isolate were presumably those described by Ferry in an earlier report of *B. bronchiseptica* infection in dogs (62). Colonies grew slowly to pinpoint size on plain agar after 48 h with gram-negative organisms having coccobacillary morphology. The isolates were motile, produced slow alkalization of litmus milk, and were negative for gelatin liquefaction, indole, and production of acid and gas from a number of carbohydrates. These characteristics fall short of today's requirements for identification of *B. bronchiseptica*.

McGowan (111) alluded to an adult male animal caretaker (case 25) from whom a culture of mucopus from the palate yielded *B. bronchiseptica*. The microbiological characteristics, as with Ferry's report, were minimal.

CONCLUSIONS

The aim of this comprehensive literature search for cases of human infection associated with *B. bronchiseptica* was to assess the propensity for disease involvement and virulence of the microorganism for humans. The taxonomic status of the microorganism, the pathological findings and probable pathogenic mechanisms associated with the agent, and the potential of *B. bronchiseptica* to act as a human commensal were examined. It is apparent that stringent criteria corresponding to those recommended by Bemis et al. (11) and Johnson and Sneath (89) for differentiating *B. bronchiseptica* from phenotypically similar oxidase-positive nonfermentative gram-negative coccobacilli were not used before the 1970s. Because of this, most case reports before that time lack a description of one or more of the characteristics needed to verify the microorganism as *B. bronchiseptica*. In several instances, the agent may have been *B. bronchiseptica* because four of the initially unverified cases were subsequently verified when we confirmed the organisms' identity.

Except for inferences that can be drawn by reviewing the pathology and pathogenic mechanisms described for *B. bronchiseptica* infections in animals and from autopsy studies of humans who died from complications of whooping cough, specific information on the pathology of human *B. bronchiseptica* infection is lacking. Studies before the 1970s of *B. bronchiseptica* as a human commensal or colonizer lack the use of appropriately stringent microbiological characteristics. Also, except in surveys of gram-negative nonfermentative bacilli isolated in microbiology laboratories, it

might be expected that isolations of *B. bronchiseptica* from healthy people would not be reported. From the information available, it appears that *B. bronchiseptica* may be isolated occasionally as a commensal or colonizer, particularly from respiratory sources. The incidence of isolation is highly dependent on the intensity of and methods used to search for the microorganism.

For this review, 25 cases of human infection thought to be associated with *B. bronchiseptica* were available for analysis, 2 from our experience and 23 from the literature. Each case was evaluated for the accuracy of the *B. bronchiseptica* identification and for the likelihood that the microorganism played a causal role. Of the 23 cases obtained from the literature review, the accuracy of *B. bronchiseptica* identification could be verified for only 8 cases. The infections encountered for the 10 verified cases (our 2 cases plus 8 from the literature review) were acute iatrogenic maxillary sinusitis (one), nosocomial tracheobronchitis (one), acute pneumonia (two), pneumonia with septicemia (one), septicemia (two), and whooping cough (three). For the whooping cough cases, it is likely that *B. bronchiseptica* acted as a colonizer and not as the cause. Of the seven remaining verified cases, six were definitely in compromised patients (three debilitated alcoholics, one with chronic lymphocytic leukemia, one with long-standing Hodgkin's disease, and one diabetic with severe epiglottitis and hypoxic brain death), and for one inadequate clinical information was presented to assess whether the patient was compromised. Only one of the seven patients was known to have had contact with a sick animal. In all of the cases, the outcome of antimicrobial treatment was difficult to assess. In case 1 the patient died as the result of severe hypoxic brain damage, while in cases 5 and 8 the patients died as a consequence of their severe hepatic disease. In case 4 the initial episode of acute bronchitis with pneumonia responded to combined amikacin and cefazolin therapy and a recrudescence shortly thereafter responded to trimethoprim-sulfamethoxazole. In case 7 the pneumonia and infected pneumothorax were treated successfully with cefazolin, a situation suggesting that the *S. aureus* recovered from both sputum and pleural drainage was the primary pathogen rather than the *B. bronchiseptica* recovered only from sputum. Case 2 represented a patient with a cervical spine fracture and postoperative aspiration pneumonia in which *B. bronchiseptica* later appeared to cause opportunistic superinfection. From recent in vitro antimicrobial susceptibility studies of *B. bronchiseptica*, the most effective agents appear to be the aminoglycosides, the antipseudomonal penicillins and broad-spectrum cephalosporins, the tetracyclines, and chloramphenicol.

The 15 cases from the literature for which the identity of *B. bronchiseptica* could not be verified comprised four patients with pneumonia, three representing compromised hosts and one with close animal contact; three children with whooping cough, each having had contact with sick animals; three animal caretakers with chronic laryngotracheitis; acute peritonitis in a patient on peritoneal dialysis having had close contact with a pet dog; meningitis in a child kicked in the head by a horse; and three inadequately described cases of two patients with endocarditis and one with acute sinusitis. For the three cases of whooping cough there were valid reasons for excluding *B. bronchiseptica* as the causative agent. In each of the remaining cases, the microbiological findings, although inadequate, did not weigh against identification of the agent as *B. bronchiseptica*. Thus, it is possible that *B. bronchiseptica* was actually involved. As with the verified cases, a compromised host was involved in many

instances, particularly when the agent seemed to be of etiological importance.

From this review, we conclude that *B. bronchiseptica* has rarely been isolated from humans despite the considerable exposure of humans to animal sources of the microorganism. Evidence suggests that the agent may occasionally be encountered as a commensal or colonizer of the human respiratory tract and, rarely, as a pathogen in human disease. When encountered as a probable pathogen, most patients have a severely compromised clinical status. Carefully planned future studies using appropriate microbiological procedures and stringent characteristics for identification of *B. bronchiseptica* are needed to determine the true incidence of the agent as a human commensal or colonizer and to evaluate further its role as an opportunistic and/or primary cause of disease.

ACKNOWLEDGMENTS

We recognize Ione Aschenbrener for her expert preparation of the manuscript. The invaluable advice of Richard T. Lally is also greatly appreciated.

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